REFERENCE 10: 137:221874

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=> d all tot l58

L58 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:555379 HCAPLUS
DN 137:114532
TI **Modafinil** compound and **cyclodextrin** mixtures
IN **Jacobs, Martin J.; Patel, Piyush R.**
PA **Cephalon, Inc., USA**
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K047-40
ICS A61K031-165
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

appl's PCT
no search rep.

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002056915	A2	20020725	WO 2001-US49189	20011219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI US 2000-256681P	P	20001219		
US 2001-23441	A	20011218		

AB Mixts. of a **modafinil** compd. with a **cyclodextrin**, methods for their use, and compns. are disclosed, along with complexes comprising a **modafinil** compd. and a **cyclodextrin** which are taste-masked and suitable for oral consumption in an aq. soln. An example of prepn. of **modafinil** in aq. 50% hydroxypropyl .beta.-**cyclodextrin** soln. was given.

ST **modafinil cyclodextrin** complex mixt soln

IT Drugs
(appetite stimulants; **modafinil** compd. and **cyclodextrin** mixts.)

IT Mental disorder
(attention deficit hyperactivity disorder; **modafinil** compd. and **cyclodextrin** mixts.)

IT Mental disorder
(cognitive; **modafinil** compd. and **cyclodextrin** mixts.)

IT Appetite
Cognition
(disorder; **modafinil** compd. and **cyclodextrin** mixts.)

IT Drug delivery systems
(elixirs; **modafinil** compd. and **cyclodextrin** mixts.)

IT Brain, disease
(ischemia; **modafinil** compd. and **cyclodextrin** mixts.)

IT **Drug bioavailability**
Fatigue, biological
Nervous system stimulants
Parkinson's disease
(**modafinil** compd. and **cyclodextrin** mixts.)

IT Inclusion compounds
RL: FMU (Formation, unclassified); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(**modafinil** compd. and **cyclodextrin** mixts.)

IT Apnea
(sleep apnea; **modafinil** compd. and **cyclodextrin** mixts.)

IT Drug delivery systems
(solids; **modafinil** compd. and **cyclodextrin** mixts.)

IT Appetite
(stimulants; **modafinil** compd. and **cyclodextrin** mixts.)

IT Brain, disease
(stroke; **modafinil** compd. and **cyclodextrin** mixts.)

IT Drug delivery systems
(syrups; **modafinil** compd. and **cyclodextrin** mixts.)

IT **443128-08-3 443128-09-4 443128-10-7 443128-11-8 443128-12-9**
RL: FMU (Formation, unclassified); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(**modafinil** compd. and **cyclodextrin** mixts.)

IT **7585-39-9DP**, .beta.-**Cyclodextrin**, ethers, complexes with **modafinil**
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**modafinil** compd. and **cyclodextrin** mixts.)

IT **7585-39-9**, .beta.-**Cyclodextrin 10016-20-3**, .alpha.-**Cyclodextrin 17465-86-0**, .gamma.-**Cyclodextrin 51166-71-3**, Dimethyl .beta.-**cyclodextrin 55216-11-0**, Trimethyl .beta.-**cyclodextrin**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**modafinil** compd. and **cyclodextrin** mixts.)

IT **68693-11-8, Modafinil**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(**modafinil** compd. and **cyclodextrin** mixts.)

L58 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:293436 HCAPLUS
DN 136:315011
TI Compositions comprising **modafinil** compounds
IN **Jacobs, Martin J.**; McIntyre, Bradley T.; **Patel, Piyush R.**
PA **Cephalon, Inc., USA**
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
IC A61K031-165; A61K009-48; A61K047-14; A61K047-26
CC 63-6 (Pharmaceuticals)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030414	A1	20020418	WO 2001-US31904	20011011
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6455588	B1	20020924	US 2000-640824	20000817
	AU 2002011677	A5	20020422	AU 2002-11677	20011011
	US 2002098240	A1	20020725	US 2001-975350	20011011
PRAI	US 2000-640824	A	20000817		
	US 2000-239490P	P	20001011		
	US 1999-150071P	P	19990820		
	WO 2001-US31904	W	20011011		

AB Particle-forming compns. of **modafinil** compds., and aq. compns. of particles, wherein the particles comprise a **modafinil** compd., are disclosed, along with methods of their prepn., and their use in the treatment of diseases. A compn. was prepd. contg 90% PEG 400, 5% Span20, and 5% Capmul MCM.
ST **modafinil** pharmaceutical compn
IT Glycerides, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, ethoxylated; compns. comprising **modafinil** compds.)
IT Diglycerides
Glycerides, biological studies
Monoglycerides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-12 monoglycerides, diglycerides and triglycerides; compns. comprising **modafinil** compds.)
IT Drugs
(appetite stimulants; compns. comprising **modafinil** compds.)
IT Mental disorder
(attention deficit hyperactivity disorder; compns. comprising **modafinil** compds.)
IT Drug delivery systems
(capsules; compns. comprising **modafinil** compds.)
IT Mental disorder
(cognitive; compns. comprising **modafinil** compds.)

IT Fatigue, biological
Nervous system stimulants
Parkinson's disease
Surfactants
(compns. comprising **modafinil** compds.)
IT Glycerides, biological studies
Monoglycerides
Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising **modafinil** compds.)
IT Appetite
Cognition
(disorder; compns. comprising **modafinil** compds.)
IT Drug delivery systems
(elixirs; compns. comprising **modafinil** compds.)
IT Drug delivery systems
(emulsions; compns. comprising **modafinil** compds.)
IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethers; compns. comprising **modafinil** compds.)
IT Castor oil
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ethoxylated; compns. comprising **modafinil** compds.)
IT Brain, disease
(ischemia; compns. comprising **modafinil** compds.)
IT Apnea
(sleep apnea; compns. comprising **modafinil** compds.)
IT Appetite
(stimulants; compns. comprising **modafinil** compds.)
IT Brain, disease
(stroke; compns. comprising **modafinil** compds.)
IT Drug delivery systems
(syrups; compns. comprising **modafinil** compds.)
IT 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 60-12-8, .beta.-Phenylethanol 98-85-1, .alpha.-Phenylethanol 100-51-6, Benzenemethanol, biological studies 108-32-7, Propylene carbonate 111-90-0, Diethylene glycol ethyl ether 538-23-8, Glyceryl tricaprylate 621-71-6, Glyceryl tricaprate 1338-39-2, Sorbitan monolaurate 1338-43-8, Sorbitan monooleate 9002-96-4, .alpha.-Tocopheryl polyethylene glycol succinate 9003-11-6, Oxirane, polymer with methyloxirane 9004-99-3, Polyoxyethylene stearate 9005-63-4D, Polyoxyethylene sorbitan, fatty acid esters 9005-65-6, Polysorbate 80 25322-68-3, Peg 25322-68-3D, Peg, ethers 26402-26-6, Glycerol monocaprylate 61909-81-7D, Hydroxystearic acid, ethoxylated 106392-12-5, Oxirane, polymer with methyloxirane, block
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising **modafinil** compds.)
IT **68693-11-8, Modafinil**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising **modafinil** compds.)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cephalon; WO 9611001 A 1996 HCAPLUS
(2) Institut Curie; WO 9925329 A 1999 HCAPLUS
(3) Laboratoire L Lafon; WO 9421371 A 1994 HCAPLUS

L58 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:293435 HCAPLUS
DN 136:315010

TI Pharmaceutical solutions of **modafinil** compounds
IN **Jacobs, Martin J.**; McIntyre, Bradley T.; **Patel, Piyush R.**
PA **Cephalon, Inc., USA**
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-165
ICS A61K047-10; A61K047-22; A61K009-00; A61K009-48
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030413	A1	20020418	WO 2001-US31685	20011011
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002099097	A1	20020725	US 2001-974473	20011010
	AU 2001096785	A5	20020422	AU 2001-96785	20011011
PRAI	US 2000-239488P	P	20001011		
	US 2001-974473	A	20011010		
	WO 2001-US31685	W	20011011		

AB Pharmaceutical compns. of **modafinil** compds., and pharmaceutical, non-aq. compns. of **modafinil** compds. in org. solvents are disclosed, along with their use in the treatment of diseases. A soln. of 95:5 PEG-400:benzyl alc. was prepd. and blood serum levels of **modafinil** was detd. in rats from the prepd. soln.

ST **modafinil** pharmaceutical soln
IT Drugs
(appetite stimulants; pharmaceutical solns. of **modafinil** compds.)
IT Mental disorder
(attention deficit hyperactivity disorder; pharmaceutical solns. of **modafinil** compds.)
IT Drug delivery systems
(capsules; pharmaceutical solns. of **modafinil** compds.)
IT Mental disorder
(cognitive; pharmaceutical solns. of **modafinil** compds.)
IT Appetite
Cognition
(disorder; pharmaceutical solns. of **modafinil** compds.)
IT Drug delivery systems
(elixirs; pharmaceutical solns. of **modafinil** compds.)
IT Brain, disease
(ischemia; pharmaceutical solns. of **modafinil** compds.)
IT Monoglycerides
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medium-chain; pharmaceutical solns. of **modafinil** compds.)
IT Fatigue, biological
Nervous system stimulants
Parkinson's disease
(pharmaceutical solns. of **modafinil** compds.)
IT Polyoxyalkylenes, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(pharmaceutical solns. of **modafinil** compds.)
IT Alcohols, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; pharmaceutical solns. of **modafinil** compds.)
IT Apnea
(sleep apnea; pharmaceutical solns. of **modafinil** compds.)
IT Drug delivery systems
(solns.; pharmaceutical solns. of **modafinil** compds.)
IT Appetite
(stimulants; pharmaceutical solns. of **modafinil** compds.)
IT Brain, disease
(stroke; pharmaceutical solns. of **modafinil** compds.)
IT Drug delivery systems
(syrups; pharmaceutical solns. of **modafinil** compds.)
IT Drug delivery systems
(unit doses; pharmaceutical solns. of **modafinil** compds.)
IT **68693-11-8, Modafinil**
RL: **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical solns. of **modafinil** compds.)
IT 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 100-51-6, Benzenemethanol, biological studies 108-32-7, Propylene carbonate 111-90-0, Diethylene glycol monoethyl ether 872-50-4, 1-Methyl-2-pyrrolidone, biological studies 5306-85-4, Dimethyl isosorbide 25322-68-3, Peg
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical solns. of **modafinil** compds.)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cephalon; WO 9611001 A 1996 HCAPLUS
(2) Cephalon; WO 0158439 A 2001 HCAPLUS
(3) Institut Curie; WO 9925329 A 1999 HCAPLUS
(4) Laboratoire L Lafon; EP 0233106 A 1987
(5) Lafon, L; US 4177290 A 1979 HCAPLUS

use CD column to separate isomers.

L58 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **2000:212699** HCAPLUS
DN **132:217021**
TI Randomized trial of **modafinil** as a treatment for the excessive daytime somnolence of narcolepsy
AU Becker, Philip M.; Jamieson, Andrew O.; Jewel, Carolyn E.; Bogan, Richard K.; James, Donna S.; Sutton, Julie T.; Corser, Bruce; Mayleben, David W.; Bernard, Shane H.; Dinner, Dubley S.; Emsellem, Helene; Knight, Elizabeth; Erwin, Charles William; Krystal, Andrew D.; Radtke, Rodney A.; Farrow, Simon; Odynski, Troy; Pinto, John; Steljes, Darlene; Feldman, Neil T.; O'Brien, Mary; Fredrickson, Paul A.; Kaplan, joseph; Lin, Siong-Chi; Burger, Charles; Fry, June M.; Guilleminault, Christian; Black, Jed; Green, Philip M.; Schmitigal, Linda; Gross, Paul T.; Dignan, Susan; Harsh, John; Hartwig, Geoffrey; Haynes, J. Brevard; Hageman, Martha; Porter-Shirley, Ken; Hertz, Gila; Hirshkowitz, Max; Moore, Constance A.; Iyer, Vasudeva; Mahowald, Mark M.; Ullevig, Constance; Mitler, Merrill M.; Hayduk, Roza; Erman, Milton K.; Pascualy, Ralph; Stolz, Sarah; Richter, Ralph W.; Gruenau, Steven P.; Webster, JoAnn J.; Ristanovic, Ruzica K.; Bergen, Donna; Kanner, Andres; Dyonzak, Jane; Rogers, Ann E.; Aldrich, Michael S.; Rosenberg, Russell; Richardson, Tim; Lee, John; Sahota, Pradeep K.; Dexter, James D.; Burger, Robert C.; Sangal, R. Bart; Sangal, JoAnne M.; Belisle, Cynthia; Schmidt, Helmut S.; Parisot, Peggy A.; Schmidt-Nowara, Wolfgang W.; Jessup, Carol; Schwartz, Jonathan R. L.; Schwartz, Elliott R.; Veit, Chris; Blakely, Liz; Scrima, Lawrence; Miller, Bradford R.; Shettar, Shashidar M.; May, Roberta S.; Wilkerson, Karen E.;

Stafford, Calvin; Grogan, Wendell A.; Tearse, Robert; Thein, Stephen G., Jr.; Colontonio, Linda; Vern, Boris A.; Mercer, Patricia J.; Merritt, Sharon L.; Walsleben, Joyce A.; O'Malley, Mary B.; Rapoport, David M.; Winokur, Andrew; Szuba, Martin D.; Civil, Richard H.; Dobbins, Thomas W.; Kribbs, Nancy Barone; Laughton, Watson B.; Nelson, Michael T.; Wang, Lixia
CS USA
SO Neurology (2000), 54(5), 1166-1175
CODEN: NEURAI; ISSN: 0028-3878
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Objective: This is one of two sep. clin. trials to evaluate the efficacy and safety of **modafinil**, a novel wake-promoting agent, in patients with excessive daytime sleepiness (EDS) assocd. with narcolepsy. Methods: In this 9-wk, randomized, placebo-controlled, double-blind, 21-center clin. trial, patients were randomized to receive fixed daily doses of **modafinil** 200 mg, **modafinil** 400 mg, or placebo. A placebo-controlled, 2-wk treatment discontinuation phase was included to evaluate the effects of withdrawal on patients who had been receiving **modafinil**. A total of 271 patients who were naive to **modafinil** received study medication in the 9-wk trial and 240 patients received study medication in the discontinuation phase. Results: Treatment with **modafinil** resulted in significant improvement in two objective measures of EDS: the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. Addnl., patient self-assessment of sleepiness was significantly improved, as measured by the Epworth Sleepiness Scale, and level of illness was significantly reduced on the independent clinician assessment, the Clin. Global Impression of Change. Nighttime sleep, monitored by nocturnal polysomnog., was not adversely effected with **modafinil** treatment compared with placebo treatment. The most frequent adverse experience was headache, which was not significantly greater for **modafinil** than placebo. During treatment discontinuation, individuals who had been receiving **modafinil** experienced a return of their EDS to baseline levels. During treatment discontinuation, patients did not experience symptoms assocd. with amphetamine withdrawal syndrome. For up to 9 wk of daily use there was no evidence for the development of dependence at the dose levels studied. Conclusion: The data indicate that **modafinil** has an excellent safety profile and is very well tolerated. **Modafinil** is an effective treatment for excessive daytime sleepiness in narcolepsy and shows continued efficacy with up to 9 wk of daily use.
ST **modafinil** narcolepsy stimulant drug withdrawal
IT Drug dependence
Drug withdrawal
Nervous system stimulants
(**modafinil** as a treatment for excessive daytime somnolence of narcolepsy in humans)
IT Sleep
(narcolepsy; **modafinil** as a treatment for excessive daytime somnolence of narcolepsy in humans)
IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**modafinil** as a treatment for excessive daytime somnolence of narcolepsy in humans)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(2) Anon; A manual of standardized terminology, techniques and scoring system

for sleep stages of human subjects 1968
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(34) Warot, D; Eur Psychiatry 1993, V8, P201

L58 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:486371 HCAPLUS
DN 131:237446
TI Determination of the D- and L-enantiomers of **modafinil** in human plasma utilizing liquid-liquid extraction and high-performance liquid chromatography
AU Gorman, Steven H.
CS Drug Safety and Disposition Department, **Cephalon**. Inc., West Chester, PA, 19380-4245, USA
SO Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 730(1), 1-7
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier Science B.V.
DT Journal
LA English
CC 1-1 (Pharmacology)
AB **Modafinil**, DLL-2-[(diphenylmethyl)sulfinyl]acetamide (**Provigil**), which is chiral at its sulfur atom, is a novel wake-promoting agent currently being developed as the racemate in the United States by Cephalon, Inc. In order to characterize the pharmacokinetic properties of each enantiomer, a stereospecific high-performance liq. chromatog. (HPLC) method has been developed for simultaneous detn. of D- and L-**modafinil** in human plasma. The analytes are extd. from plasma into a mixt. of hexane-methylene chloride-triethylamine (55:45:2, vol./vol./v) and then resolved on an EM

Sepns. ChiraDex .beta.-**cyclodextrin** column at 12.degree. using an isocratic mobile phase of 0.020 M, pH 3.0 phosphate buffer--acetonitrile (84:14, vol./vol.). D- And L-**modafinil**, and the internal std., 3,3-diphenylpropylamine, are monitored by UV detection at 225 nm. The two major circulating metabolites, **modafinil** acid and **modafinil** sulfone, have been shown not to interfere with the assay. Using 0.200 mL of plasma for extn., the quantifiable range of the assay is 0.100 to 15.0 .mu.g/mL for each enantiomer. The utility of the assay for the characterization of D- and L-**modafinil** pharmacokinetics in humans after single and multiple oral doses of racemic **modafinil** has been demonstrated.

ST **modafinil** enantiomer blood extn liq chromatog; HPLC extn **modafinil** enantiomer blood

IT Blood analysis
HPLC
Solvent extraction
(detn. of D- and L-enantiomers of **modafinil** in human plasma utilizing liq.-liq. extn. and high-performance liq. chromatog.)

IT **112111-43-0 112111-47-4**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of D- and L-enantiomers of **modafinil** in human plasma utilizing liq.-liq. extn. and high-performance liq. chromatog.)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L58 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AN **1999:345577** HCAPLUS

DN **131:164947**

TI Open-label, single-dose pharmacokinetic study of **modafinil** tablets: Influence of age and gender in normal subjects

AU Wong, Y. Nancy; King, S. Peter; Simcoe, Donna; Gorman, Steve; Laughton, Watson; McCormick, George C.; Grebow, Peter

CS **Cephalon, Inc., West Chester, PA, USA**

SO Journal of Clinical Pharmacology (1999), 39(3), 281-288
CODEN: JCPCBR; ISSN: 0091-2700

PB Sage Publications

DT Journal

LA English

CC 1-2 (Pharmacology)

AB An open-label, single-center, single-dose, parallel-group study was performed in healthy young males and females as well as healthy elderly males to examine the influence of age and gender on the pharmacokinetics of **modafinil** following administration of a single 200 mg oral dose. Twelve subjects were enrolled in each of the following three groups: young males, young females, and elderly males. Each fasted (overnight) subject received 2.times.100 mg **modafinil** tablets. Blood and urine samples were collected at various times up to 72 h postdose for the detn. of plasma and urine levels of **modafinil** as well as the acid and sulfone metabolites. The plasma concns. of the individual isomers, d- and l-**modafinil**, were also detd. Pharmacokinetic parameters were detd. by noncompartmental methods. **Modafinil** was well tolerated at a single oral dose of 200 mg. The most commonly reported adverse events were headache, fever, pharyngitis, and asthenia. There were no clin. meaningful differences with respect to

the incidence rate of treatment-emergent adverse events among the young female, young male, and old male groups. **Modafinil** was rapidly absorbed after oral dosing and slowly cleared (t1/2 .apprx. 11-14 h) from the body. **Modafinil** acid was the major urinary metabolite, which accounted for 35% to 60% of the dose. Results from this study indicated that there were age and gender effects on **modafinil** clearance processes. In this regard, the clearance rate of **modafinil** in males decreased with age while young females cleared **modafinil** at a faster rate than young males. Stereospecific pharmacokinetics of **modafinil** were also demonstrated. The d-**modafinil** was eliminated three times faster than the l-**modafinil**.

ST **modafinil** pharmacokinetics age gender

IT Aging, animal
Pharmacokinetics
Sex
(pharmacokinetic study of **modafinil** tablets and influence of age and gender in normal human subjects)

IT **68693-11-8, Modafinil**
RL: **BPR (Biological process)**; **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetic study of **modafinil** tablets and influence of age and gender in normal human subjects)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(12) Lin, J; Neurobiology 1996, V93, P14128 HCAPLUS
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L58 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AN **1999:339163** HCAPLUS

dosages

DN **131:164943**

TI A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of **modafinil** tablets in healthy male volunteers

AU Wong, Y. Nancy; Simcoe, Donna; Hartman, Linda N.; Laughton, Watson B.; King, S. Peter; McCormick, George C.; Grebow, Peter E.

CS Drug Safety and Disposition, **Cephalon**, Inc., West Chester, PA, USA

SO Journal of Clinical Pharmacology (1999), 39(1), 30-40
CODEN: JCPCBR; ISSN: 0091-2700

PB Sage Publications
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 63
AB A randomized, double-blind, placebo-controlled, ascending-dose study was conducted to evaluate the pharmacokinetic and safety profiles of increasing **modafinil** doses (200 mg, 400 mg, 600 mg, 800 mg) administered orally over a 7-day period in normal healthy male volunteers. Eight subjects (six **modafinil**; two placebo) were randomized to each of the four dose groups. **Modafinil** or a placebo was administered once daily for 7 days. Serial blood samples were obtained following administration of the day 1 and day 7 doses for characterization of pharmacokinetics, and trough samples were obtained prior to dosing on days 2 through 6 to assess the time to reach the steady state. Pharmacokinetic parameters were calcd. using noncompartmental methods. **Modafinil** steady state was reached after three daily doses. **Modafinil** pharmacokinetics were dose and time independent over the range of 200 mg to 800 mg. Steady-state pharmacokinetics of **modafinil** were characterized by a rapid oral absorption rate, a low plasma clearance of .apprx.50 mL/min, a vol. of distribution of .apprx.0.8 L/kg, and a long half-life of .apprx.15 h. **Modafinil** was primarily eliminated by metab. **Modafinil** acid was the major urinary metabolite. Stereospecific pharmacokinetics of **modafinil** were demonstrated. The d-**modafinil** enantiomer was eliminated at a threefold faster rate than l-**modafinil**. **Modafinil** 200 mg, 400 mg, and 600 mg doses were generally well tolerated. The **modafinil** 800 mg dose panel was discontinued after 3 days of treatment due to the observation of increased blood pressure and pulse rate. The safety data from this study suggest that the max. tolerable single daily oral **modafinil** dose, without titrn., may be 600 mg.
ST pharmacokinetics tolerability **modafinil** tablet
IT Drug delivery systems
(tablets; pharmacokinetics and tolerability of **modafinil** tablets in healthy men)
IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified);** BIOL (Biological study); PROC (Process)
(pharmacokinetics and tolerability of **modafinil** tablets in healthy men)
IT 63547-24-0, **Modafinil** acid **112111-43-0** **112111-47-4** 118779-53-6
RL: **BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation);** BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(pharmacokinetics and tolerability of **modafinil** tablets in healthy men)
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L58 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:291690** HCAPLUS
DN **129:35973**
TI **Modafinil**: a review of its pharmacology and clinical efficacy in the management of narcolepsy
AU Mcclellan, Karen J.; Spencer, Caroline M.
CS Adis International Limited, Auckland, N. Z.
SO CNS Drugs (1998), 9(4), 311-324
CODEN: CNDREF; ISSN: 1172-7047
PB Adis International Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 63 refs. **Modafinil** promotes wakefulness through an as-yet-unknown mechanism of action. It increases daytime sleep latency and reduces excessive daytime sleepiness (EDS) in patients with narcolepsy. However, the drug does not suppress cataplexy. Although direct comparative data are lacking, **modafinil** offers advantages over amphetamines and methylphenidate in patients with narcolepsy because of its lack of rebound phenomena after treatment withdrawal and its low abuse potential. Clin. trials have shown **modafinil** to be well tolerated in patients with narcolepsy. Except for headache, which was reported with an increased frequency in **modafinil** recipients, the tolerability profile of **modafinil** at 200-400 mg/day was similar to that of placebo in patients treated for 9 wk. Preliminary data suggest that the tolerability of **modafinil** is maintained for a long term (40 wk). Thus, **modafinil** is effective in the treatment of EDS in patients with narcolepsy, although it is not effective against cataplexy. Preliminary findings indicate that, unlike other psychostimulants, the drug is unlikely to be abused and is not assocd. with withdrawal phenomena. Therefore, **modafinil** is likely to be an effective therapeutic option for the treatment of EDS in patients with narcolepsy.
ST review **modafinil** narcolepsy treatment; sleep paroxysmal **modafinil** treatment review
IT Sleep
(narcolepsy; **modafinil** treatment of human)
IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(narcolepsy of humans treatment by)

L58 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:162183** HCAPLUS
DN **128:238869**
TI Treatment modalities for narcolepsy
AU Fry, June M.
CS Division of Somnology, Department of Neurology, Allegheny University of

Health Sciences, Philadelphia, PA, 19129, USA
SO Neurology (1998), 50(2, Suppl. 1), S43-S48
CODEN: NEURAI; ISSN: 0028-3878
PB Lippincott-Raven Publishers
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 25 refs. Narcolepsy, a lifelong disorder, requires long-term management of symptoms. Interventions may be nonpharmacol., such as lifestyle changes, and pharmacol. for relief of daytime sleepiness. Pharmacol. treatment of narcolepsy has depended on the use of CNS stimulants to increase wakefulness, vigilance, and performance. The medications considered effective in the treatment of narcolepsy include dextroamphetamine, pemoline, methylphenidate, methamphetamine, and **modafinil**; only methylphenidate hydrochloride and dextroamphetamine are approved for use in the United States. The currently available stimulants are assocd. with sympathomimetic side effects, limitations in efficacy, and neg. effects on nighttime sleep. This has led to the development of alternative agents. **Modafinil**, a new wake-promoting agent, has been shown to be effective in reducing daytime sleepiness in patients with narcolepsy. The results of a United States 18-center randomized, placebo-controlled, 9-wk trial of **modafinil** in the treatment of patients with narcolepsy has recently been reported. Patients receiving **modafinil** demonstrated significant improvement in all subjective and objective measures of sleepiness. Treatment with **modafinil** 200 mg and 400 mg daily significantly reduced mean scores on the Epworth Sleepiness Scale compared with baseline and placebo ($p < 0.001$) and significantly increased mean scores on the Maintenance of Wakefulness Test ($p < 0.001$) and the Multiple Sleep Latency Test ($p < 0.01$) compared with baseline and placebo. More improvement, as recorded on the Clin. Global Impression of Change scale, was seen in the **modafinil** group than in the placebo group at all time points ($p < 0.001$). **Modafinil** was well tolerated, with headache the only adverse event to occur significantly more often in the active treatment group ($p < 0.05$). These results suggest that **modafinil** is an important new therapeutic option for the treatment of narcolepsy.
ST narcolepsy stimulant review
IT Sleep
(narcolepsy; treatment modalities for narcolepsy in humans)
IT Nervous system stimulants
(treatment modalities for narcolepsy in humans)

L58 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:77585** HCAPLUS
DN **128:200937**
TI Randomized trial of **modafinil** for the treatment of pathological somnolence in narcolepsy
CS US Modafinil in Narcolepsy Multicenter Study Group, USA
SO Annals of Neurology (1998), 43(1), 88-97
CODEN: ANNED3; ISSN: 0364-5134
PB Lippincott-Raven Publishers
DT Journal
LA English
CC 1-11 (Pharmacology)
AB This placebo-controlled, double-blind, randomized, parallel-group, 18-center study assessed the efficacy and safety of **modafinil**, a new wake-promoting drug for treating sleepiness in narcolepsy. Subjects with narcolepsy ($n = 283$) received daily **modafinil**, 200 or 400 mg, or placebo, for 9 wk, followed by an open-label treatment period. Subjective sleepiness was measured with the Epworth Sleepiness Scale. Objective sleepiness was assessed with the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. Level of illness was measured with

the Clin. Global Impression of Change. **Modafinil** significantly reduced all measures of sleepiness and was assocd. with significant improvements in level of illness. Medication-related adverse experiences were few, dose-dependent, and mostly rated mild to moderate. **Modafinil** taken once daily was a very well tolerated and effective wake-promoting agent in the treatment of excessive daytime somnolence assocd. with narcolepsy. **Modafinil** demonstrated an excellent safety profile for up to 40 wk of open-label treatment and efficacy was maintained, suggesting that tolerance will not develop with long-term use. **Modafinil** is a pharmacol. and clin. promising compd. for the treatment of pathol. daytime somnolence.

ST **modafinil** treatment somnolence narcolepsy

IT Sleep
(narcolepsy; **modafinil** for treatment of pathol. somnolence in narcolepsy in humans)

IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**modafinil** for treatment of pathol. somnolence in narcolepsy in humans)

L58 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1998:30931** HCAPLUS
DN **128:188537**
TI **Modafinil**: a novel stimulant for the treatment of narcolepsy
AU Scammell, Thomas E.; Matheson, Jean
CS Department of Neurology, Sleep Disorders Program, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, 02215, USA
SO Expert Opinion on Investigational Drugs (1998), 7(1), 99-112
CODEN: EOIDER; ISSN: 0967-8298
PB Ashley Publications
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Excessive daytime sleepiness (EDS) is a common and debilitating symptom of narcolepsy and other sleep disorders. **Modafinil** is a novel stimulant which effectively treats EDS, yet lacks many of the undesirable side-effects commonly encountered with currently available compds. The specific mode of action of **modafinil** is not well understood, but it may promote sleep by indirectly influencing adrenergic or GABAergic neurotransmission. **Modafinil**-induced wakefulness is not assocd. with rebound hypersomnolence or the potential for abuse as is often encountered with other stimulants such as amphetamines. At typical therapeutic doses, **modafinil** may produce dry mouth but generally has a low incidence of minor side-effects. Many preclin. and clin. studies have demonstrated the effectiveness of **modafinil** in promoting wakefulness and vigilance in normal subjects and in those with EDS. **Modafinil** significantly improves the EDS of narcolepsy and also may improve the EDS of idiopathic hypersomnia and obstructive sleep apnoea. **Modafinil**'s low prevalence of side-effects, minimal potential for abuse, and lack of rebound hypersomnia indicate that it has potential to become a widely prescribed drug for the treatment of narcolepsy.

ST **modafinil** stimulant narcolepsy

IT Nervous system stimulants
(**modafinil** as a novel stimulant for the treatment of narcolepsy in humans)

IT Sleep
(narcolepsy; **modafinil** as a novel stimulant for the treatment of narcolepsy in humans)

IT **68693-11-8, Modafinil**
RL: BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(**modafinil** as a novel stimulant for the treatment of narcolepsy in humans)

L58 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:605135** HCAPLUS
DN **127:243197**
TI Randomized, double-blind, placebo-controlled crossover trial of **modafinil** in the treatment of excessive daytime sleepiness in narcolepsy
AU Broughton, R. J.; Fleming, J. A. E.; George, C. F. P.; Hill, J. D.; Kryger, M. H.; Moldofsky, H.; Montplaisir, J. Y.; Morehouse, R. L.; Moscovitch, A.; Murphy, W. F.
CS Ottawa General Hospital, Ottawa, ON, K1H 8L6, Can.
SO Neurology (1997), 49(2), 444-451
CODEN: NEURAI; ISSN: 0028-3878
PB Lippincott-Raven
DT Journal
LA English
CC 1-11 (Pharmacology)
AB Seventy-five patients meeting international diagnostic criteria for narcolepsy enrolled in a 6-wk, three-period, randomized, crossover, placebo-controlled trial. Patients received placebo, **modafinil** 200 mg, or **modafinil** 400 mg in divided doses (morning and noon). Evaluations occurred at baseline and at the end of each 2-wk period. Compared with placebo, **modafinil** 200 and 400 mg significantly increased the mean sleep latency on the Maintenance of Wakefulness Test by 40% and 54%, with no significant difference between the two doses. **Modafinil**, 200 and 400 mg, also reduced the combined no. of daytime sleep episodes and periods of severe sleepiness noted in sleep logs. The likelihood of falling asleep as measured by the Epworth Sleepiness Scale was equally reduced by both **modafinil** dose levels. There were no effects on nocturnal sleep initiation, maintenance, or architecture, nor were there any effects on sleep apnea or periodic leg movements. Neither dose interfered with the patients' ability to nap voluntarily during the day nor with their quantity or quality of nocturnal sleep. **Modafinil** produced no changes in blood pressure or heart rate in either normotensive or hypertensive patients. The only significant adverse effects were seen at the 400-mg dose, which was assocd. with more nausea and more nervousness than either placebo or the 200-mg dose. As little as a 200-mg daily dose of **modafinil** is therefore an effective and well-tolerated treatment of excessive daytime somnolence in narcoleptic persons.
ST **modafinil** narcolepsy sleep
IT Sleep
(**modafinil** in the treatment of excessive daytime sleepiness in narcolepsy)
IT Sleep
(narcolepsy; **modafinil** in the treatment of excessive daytime sleepiness in narcolepsy)
IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**modafinil** in the treatment of excessive daytime sleepiness in narcolepsy)

L58 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:262706** HCAPLUS
DN **126:308803**
TI Acetamide derivative having defined particle size
IN Grebow, Peter E.; Corvari, Vincent; Stong, David

PA **Cephalon, Inc., USA**
SO U.S., 13 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K009-14
ICS A61K031-16
NCL 514618000
CC 63-5 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5618845	A	19970408	US 1994-319124	19941006
	GB 2293103	A1	19960320	GB 1995-24328	19951004
	GB 2293103	B2	19970507		
	CA 2201967	AA	19960418	CA 1995-2201967	19951004
	WO 9611001	A1	19960418	WO 1995-US12944	19951004
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9539514	A1	19960502	AU 1995-39514	19951004
	AU 703087	B2	19990318		
	EP 731698	A1	19960918	EP 1995-937389	19951004
	EP 731698	B1	20000112		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09511754	T2	19971125	JP 1995-512675	19951004
	JP 2915146	B2	19990705		
	BR 9509257	A	19980707	BR 1995-9257	19951004
	HU 77778	A2	19980828	HU 1998-737	19951004
	EP 966962	A1	19991229	EP 1999-202603	19951004
	EP 966962	B1	20010221		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	AT 188607	E	20000115	AT 1995-937389	19951004
	ES 2142499	T3	20000416	ES 1995-937389	19951004
	AT 199216	E	20010315	AT 1999-202603	19951004
	EP 1088549	A1	20010404	EP 2000-125091	19951004
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	ES 2156457	T3	20010616	ES 1999-202603	19951004
	RU 2171674	C2	20010810	RU 1997-108161	19951004
	PL 181523	B1	20010831	PL 1995-319480	19951004
	LT 4303	B	19980325	LT 1997-60	19970403
	FI 9701417	A	19970404	FI 1997-1417	19970404
	NO 9701541	A	19970604	NO 1997-1541	19970404
	LV 11852	B	19980320	LV 1997-55	19970404
	AU 9935090	A1	19990819	AU 1999-35090	19990616
	AU 729586	B2	20010208		
PRAI	US 1994-319124	A	19941006		
	AU 1995-39514	A3	19951004		
	EP 1995-937389	A3	19951004		
	EP 1999-202603	A3	19951004		
	WO 1995-US12944	W	19951004		

AB Pharmaceutical compns. comprising **modafinil** (I) in the form of particles of defined size (95% of total particle having diam. .ltoreq.200 .mu.m) are claimed. The particle size of **modafinil** can have a significant effect on the potency and safety profile of the drug. I powder having mean particle size of 50.18 .mu.m has faster dissoln. rate than those having mean particle size of 94.05 .mu.m and had plasma conc. of 10 .mu.g/mL as compared with 8.mu.g/mL.

ST acetamide deriv particle size pharmaceutical; **modafinil** particle

size pharmaceutical safety
IT Dissolution rate
Drug delivery systems
Particle size
(acetamide deriv. having defined particle size)
IT Sleep
(narcolepsy; acetamide deriv. having defined particle size)
IT **68693-11-8, Modafinil**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(acetamide deriv. having defined particle size)

L58 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:182190** HCAPLUS
DN **126:258244**
TI **Modafinil: Modiodal**
AU Rochegude, S.; Constant, H.
CS Pharmacie, Hoptial Debrousse, Lyon, 69322, Fr.
SO Lyon Pharmaceutique (1996), 47(7), 363-366
CODEN: LYPHAD; ISSN: 0024-7804
PB Elsevier
DT Journal; General Review
LA French
CC 1-0 (Pharmacology)
AB A review, with no refs. The pharmacodynamics, pharmacokinetics, and dosage of **modafinil** are discussed for treatment of narcolepsy or idiopathic hypersomnia.
ST **modafinil** pharmacodynamics pharmacokinetics narcolepsy hypersomnia review; **Modiodal** pharmacodynamics pharmacokinetics narcolepsy hypersomnia review
IT Sleep
(disorder, hypersomnia; **modafinil** pharmacodynamics and pharmacokinetics and use for treatment of narcolepsy or hypersomnia)
IT Nervous system stimulants
(**modafinil** pharmacodynamics and pharmacokinetics and use for treatment of narcolepsy or hypersomnia)
IT Sleep
(narcolepsy; **modafinil** pharmacodynamics and pharmacokinetics and use for treatment of narcolepsy or hypersomnia)
IT **68693-11-8, Modafinil**
RL: BAC (Biological activity or effector, except adverse); **BPR (Biological process); BSU (Biological study, unclassified);** THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**modafinil** pharmacodynamics and pharmacokinetics and use for treatment of narcolepsy or hypersomnia)

L58 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1997:75025** HCAPLUS
DN **126:139338**
TI Clinical assessment of **modafinil**
AU Laffont, F.
CS Unite de Sommeil, Pitie-Salpetriere Hospital Group, Paris, 75651, Fr.
SO Drugs of Today (1996), 32(Suppl. I, Modafinil: A New Treatment for Narcolepsy), 35-44
CODEN: MDACAP; ISSN: 0025-7656
PB Prous
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 27 refs. Very troublesome for patients in their social and occupational activities, daytime sleepiness is a cause of a large no. of accidents. The first treatment is chronobiol. and excessively long

working hours must be avoided. Intentional naps planned over the day improve alertness of patients. Nevertheless, patients must be treated in order to recover a normal life. Amphetamines are certainly effective, but have notable adverse effects and are assocd. with a risk of addiction. **Modafinil** has been prescribed officially in France since Sept. 1994 for the treatment of daytime sleepiness in patients with narcolepsy and idiopathic hypersomnia. Therapeutic efficacy in these conditions has been confirmed; the percentage of responders is about 70%. Safety and acceptability is excellent, adverse effects are minimal, and no evidence has been found of intolerance regarding lab. parameters and liver function in particular. No subjective disturbance of sleep has been reported and no evidence suggesting dependence has been found following sudden withdrawal. **Modafinil** enables patients to to regain a school, family, social and occupational existence close to normal.

ST review **modafinil** nervous system stimulant

IT Nervous system stimulants
(clin. assessment of **modafinil** in humans)

IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. assessment of **modafinil** in humans)

L58 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1996:491464** HCAPLUS
DN **125:131453**
TI Clinical assessment of **modafinil**
AU Laffont, F.
CS Unite de Sommeli, Pitie-Salpetriere Hospital Group, Paris, 75651/13, Fr.
SO Drugs of Today (1996), 32(4), 339-347
CODEN: MDACAP; ISSN: 0025-7656
PB Prous
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 27 refs. Very troublesome for patients in their social and occupational activities, daytime sleepiness is a cause of a large no. of accidents. The first treatment is chronobiol. and excessively long working hours must be avoided. Intentional naps planned over the day improve alertness of patients. Nevertheless, patients must be treated in order to recover a normal life. Amphetamines are certainly effective, but have notable adverse effects and are assocd. with a risk of addiction. **Modafinil** has been prescribed officially in France since Sept. 1994 for the treatment of daytime sleepiness in patients with narcolepsy and idiopathic hypersomnia. Therapeutic efficacy in these conditions has been confirmed; the percentage of responders is about 70%. Safety and acceptability is excellent, adverse effects are minimal, and no evidence has been found of intolerance regarding lab. parameters and liver function in particular. No subjective disturbance of sleep has been reported and no evidence suggesting dependence has been found following sudden withdrawal. **Modafinil** enables patients to to regain a school, family, social and occupational existence close to normal.

ST **modafinil** review

IT **68693-11-8, Modafinil**
RL: **ADV (Adverse effect, including toxicity)**; BAC (Biological activity or effector, except adverse); **BSU (Biological study, unclassified)**; THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. assessment of **modafinil** in humans)

L58 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN **1996:491460** HCAPLUS

DN **125:157486**
TI Pharmacokinetic profile of **modafinil**
AU Moachon, G.; Kanmacher, I.; Clenet, M.; Matinier, D.
CS Centre de Recherches du Laboratoire L. Lafon, Maisons-Alfort, 94701, Fr.
SO Drugs of Today (1996), 32(4), 327-337
CODEN: MDACAP; ISSN: 0025-7656
PB Prous
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 9 refs. The pharmacokinetics of **modafinil** have been studied in mouse, rat, rabbit, dog and humans in a large range of doses. In humans **modafinil** exhibits linear kinetics, with plasma concns. and AUC increasing proportionally with dose after either single or repeated administration. The percentage of unchanged **modafinil** excreted in the urine is low (<10% of the administered dose). The main metabolite, **modafinil** acid, is inactive and excreted unconjugated in the urine.
ST review pharmacokinetics **modafinil**
IT **68693-11-8, Modafinil**
RL: **BPR (Biological process); BSU (Biological study, unclassified)**; BIOL (Biological study); PROC (Process)
(pharmacokinetic profile of **modafinil**)

L58 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:686623 HCAPLUS
DN 121:286623
TI Extrusion and freeze-drying method for preparing pharmaceutical particles
IN Nguyen, Thanh-Tam; Jacquot-Leyder, Joelle
PA Laboratoire L. Lafon, Fr.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA French
IDS
IC ICM B01J013-04
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9421371	A1	19940929	WO 1994-FR281	19940315
	W: CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FR 2702968	A1	19940930	FR 1993-3316	19930323
	FR 2702968	B1	19950623		
	CA 2156915	AA	19940929	CA 1994-2156915	19940315
	EP 690747	A1	19960110	EP 1994-909968	19940315
	EP 690747	B1	19970528		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 08507940	T2	19960827	JP 1994-520710	19940315
	AT 153562	E	19970615	AT 1994-909968	19940315
	ES 2105663	T3	19971016	ES 1994-909968	19940315
	US 5843347	A	19981201	US 1997-906004	19970804
PRAI	FR 1993-3316		19930323		
	WO 1994-FR281		19940315		
	US 1995-530293		19950919		

AB A method for prepg. particles each of which consists of a carrier forming a matrix, and at least one active ingredient uniformly distributed throughout said matrix. The method comprises extrusion and freeze-drying steps, wherein (1) at least one active ingredient, a physiol. acceptable hydrophilic carrier, and water are uniformly mixed to give a pasty mixt. with a viscosity at room temp. (15-20.degree.) of under 1 Pa.s; (2) the resulting uniform mixt. is extruded and the extrudate is broken up into moist particles; (3) the resulting particles are frozen as they fall under

their own wt. into an inert gas stream at a below-zero temp.; and (4) said particles are freeze-dried. A mixt. of paracetamol 100.00, dextran 10.00, xanthan 0.05, lactose 15.000, polysorbate-60 0.40 and water 120.00 g was extruded to particles of 0.5 mm diam. which were then freeze-dried under N.

ST paracetamol freeze dried pharmaceutical

IT Gelatins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(extrusion and freeze-drying method for prepg. pharmaceutical particles)

IT Pharmaceutical dosage forms
(freeze-dried, extrusion and freeze-drying method for prepg. pharmaceutical particles)

IT 50-99-7, Glucose, biological studies 56-40-6, Glycocol, biological studies 57-50-1, Saccharose, biological studies 63-42-3, Lactose 69-65-8, Mannitol 79-10-7D, Acrylic acid, polymers 79-41-4D, Methacrylic acid, polymers 103-90-2, Paracetamol 108-73-6, Phloroglucinol 846-49-1, Lorazepam 3239-44-9, Dexfenfluramine 3505-38-2, Carbinoxamine maleate 6964-20-1, Tiadenol **7585-39-9**, .beta.-**Cyclodextrin 7585-39-9D**, .beta.-**Cyclodextrin**, hydroxypropyl ethers 7631-86-9, Silica, biological studies 9000-01-5, Gum arabic 9000-65-1, Tragacanth Gum 9000-69-5, Pectins 9003-39-8, Pvp 9004-32-4, Cmc 9004-34-6, Cellulose, biological studies 9004-34-6D, Cellulose, ethers 9004-53-9, Dextrin 9004-54-0, Dextran, biological studies 9005-32-7D, Alginic acid, derivs. 9012-76-4, Chitosan 9050-36-6, Maltodextrin 11138-66-2, Xanthan **12619-70-4**, **Cyclodextrin** 23288-49-5, Probucol 25086-15-1, Eudragit l 100 25322-68-3, Peg 36322-90-4, Piroxicam **51166-71-3**, Dimethyl .beta.-**cyclodextrin** 52519-63-8D, Carboxymethylchitin, ethers 53179-11-6, Loperamide **68693-11-8**, **Modafinil** 82101-10-8, Flerobuterol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(extrusion and freeze-drying method for prepg. pharmaceutical particles)

=> fil embase
FILE 'EMBASE' ENTERED AT 15:29:29 ON 09 OCT 2002

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L102 ANSWER 1 OF 10 EMBASE
AN **2002288187** EMBASE
TI Improvement of learning processes following chronic systemic administration of **modafinil** in mice.
AU Beracochea D.; Celerier A.; Borde N.; Valleau M.; Peres M.; Pierard C.
CS D. Beracochea, Lab. de Neurosciences Cognitives, UMR CNRS 5106, Universite de Bordeaux 1, Avenue des Facultes, 33405 Talence Cedex, France. d.beracochea@neurocog.u-bordeaux.fr
SO Pharmacology Biochemistry and Behavior, (2002) 73/3 (723-728).
Refs: 31
ISSN: 0091-3057 CODEN: PBBHAU
PUI S 0091-3057(02)00877-8
CY United States
DT Journal; Article

FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB This study was aimed at determining the effects of a chronic **modafinil** intraperitoneal administration on the rate of learning in a series of five serial spatial discrimination reversals (SSDR) in a T-maze. Results showed that a daily **modafinil** administration at 64 mg/kg but not at 32 mg/kg induced a faster learning rate as compared to controls. This learning improvement in experimental mice was due to the faster emergence of a win-stay rule over days of testing. In contrast, a second experiment showed that the same **modafinil** treatment had no significant effect on contingently reinforced alternation rates over five successive days of testing, as compared to controls. Thus, the results show that **modafinil** spared the ability to shift responses over trials and consequently, that the use of the win-stay rule to solve the SSDR task observed in **modafinil**-treated animals is due to an improvement of learning processes.
CT Medical Descriptors:
*learning
drug effect
spatial discrimination
maze test
task performance
habituation
animal behavior
nonhuman
male
mouse
animal experiment
controlled study
article
priority journal
Drug Descriptors:
***modafinil: PD, pharmacology**
***modafinil: IP, intraperitoneal drug administration**
RN **(modafinil) 68693-11-8**

L102 ANSWER 2 OF 10 EMBASE
AN **2002118666** EMBASE
TI Steady-state pharmacokinetics and tolerability of **modafinil** administered alone or in combination with dextroamphetamine in healthy volunteers.
AU Hellriegel E.T.; Arora S.; Nelson M.; Robertson Jr. P.
CS Dr. P. Robertson Jr., Cephalon, Inc., 145 Brandywine Parkway, West Chester, PA 19380, United States
SO Journal of Clinical Pharmacology, (2002) 42/4 (450-460).
Refs: 21
ISSN: 0091-2700 CODEN: JCPCBR
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The potential for a drug-drug interaction between **modafinil** and dextroamphetamine, each at steady state, was investigated in an open-label, randomized, single-period study in 32 healthy male and female volunteers. All subjects received **modafinil** orally once daily for 28 days (200 mg on Days 1-7; 400 mg on Days 8-28). On Days 22 to 28,

half of the subjects also received dextroamphetamine (20 mg) orally 7 hours after **modafinil**. Samples for pharmacokinetic (PK) profiling were obtained on Days 21 and 28. The mean changes in PK parameters for **modafinil** and its two circulating metabolites between the two groups were not statistically significantly different, except C(max) for **modafinil** acid. Adverse events obtained in the two groups were similar and mild or moderate in nature. The results indicate that administration of low-dose dextroamphetamine in this dosing regimen does not alter the steady-state pharmacokinetics of **modafinil**. The combination has a similar tolerability profile as **modafinil** alone. .COPYRGT. 2002 the American College of Clinical Pharmacology.

CT Medical Descriptors:
*narcolepsy: DT, drug therapy
*drug potentiation
steady state
metabolite
drug blood level
drug absorption
dose response
drug tolerability
nausea: SI, side effect
headache: SI, side effect
insomnia: SI, side effect
vertigo: SI, side effect
anorexia: SI, side effect
nervousness
anxiety
peripheral vascular disease: SI, side effect
asthenia: SI, side effect
gastrointestinal symptom: SI, side effect
human
male
female
major clinical study
clinical trial
randomized controlled trial
controlled study
adult
article
Drug Descriptors:
***modafinil: AE, adverse drug reaction**
***modafinil: CT, clinical trial**
***modafinil: CB, drug combination**
***modafinil: CR, drug concentration**
***modafinil: IT, drug interaction**
***modafinil: DT, drug therapy**
***modafinil: PK, pharmacokinetics**
***modafinil: PO, oral drug administration**
*dexamphetamine: CB, drug combination
*dexamphetamine: CR, drug concentration
*dexamphetamine: IT, drug interaction
*dexamphetamine: DT, drug therapy
*dexamphetamine: PK, pharmacokinetics
*dexamphetamine: PO, oral drug administration
RN **(modafinil) 68693-11-8**; (dexamphetamine) 1462-73-3, 51-63-8, 51-64-9
CN **Provigil**

L102 ANSWER 3 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000213815 EMBASE
TI Evaluation of the abuse liability of **modafinil** and other drugs for excessive daytime sleepiness associated with narcolepsy.

AU Jasinski D.R.; Kovacevic-Ristanovic R.
CS R. Kovacevic-Ristanovic, Department of Neurological Sciences, Rush-Presbyt.-St. Luke's Med. Ctr., 1725 West Harrison St., Chicago, IL 60612-3824, United States
SO Clinical Neuropharmacology, (2000) 23/3 (149-156).
Refs: 50
ISSN: 0362-5664 CODEN: CLNEDB
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
040 Drug Dependence, Alcohol Abuse and Alcoholism
LA English
SL English
AB Psychostimulants have been used routinely for the treatment of the disabling daytime sleepiness associated with narcolepsy. However, the perceived and real potential for abuse of amphetamine and amphetamine-like stimulants prompted a search for new wake-promoting compounds with lower dependency and abuse liabilities. **Modafinil** is a novel wake-promoting agent with a mechanism of action that differs markedly from that of amphetamine and amphetamine-like stimulants. In controlled clinical trials, **modafinil** has been shown to be an effective and well-tolerated treatment for excessive daytime sleepiness (EDS) in patients with narcolepsy. With a benzhydrylsulfinylacetamide structure, **modafinil** has a low level of solubility in water (<1 mg/mL) and is unstable at temperatures .gtoreq.180.degree.C, physicochemical properties that reduce the potential for its abuse via intravenous injection and smoking, respectively. Available preclinical and clinical data on the abuse liability of **modafinil** suggest a much lower potential for abuse and dependency than amphetaminelike stimulants commonly used for treating EDS in patients with narcolepsy. Therefore, **modafinil** represents a valuable therapeutic option for the treatment of EDS associated with narcolepsy.
CT Medical Descriptors:
*narcolepsy
*drug abuse
*somnolence: DT, drug therapy
disease association
drug dependence
drug efficacy
drug tolerability
drug solubility
drug stability
human
nonhuman
male
female
mouse
rat
clinical trial
randomized controlled trial
double blind procedure
crossover procedure
controlled study
article
priority journal
Drug Descriptors:
***modafinil: CT, clinical trial**
***modafinil: DT, drug therapy**
***modafinil: PR, pharmaceutics**
***modafinil: PO, oral drug administration**
*amphetamine

*amphetamine derivative
methamphetamine
methylphenidate: PO, oral drug administration
pemoline magnesium
dexamphetamine
RN (**modafinil**) **68693-11-8**; (amphetamine) 1200-47-1, 139-10-6, 156-34-3, 2706-50-5, 300-62-9, 51-62-7, 60-13-9, 60-15-1; (methamphetamine) 28297-73-6, 51-57-0, 537-46-2, 7632-10-2; (methylphenidate) 113-45-1, 298-59-9; (pemoline magnesium) 18968-99-5; (dexamphetamine) 1462-73-3, 51-63-8, 51-64-9
CN (1) Dexedrine; (2) Desoxyn; (3) Ritalin; (4) Cylert
CO (1) SmithKline Beecham (United States); (3) Novartis (United States); (4) Abbott (United States)

L102 ANSWER 4 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999219177 EMBASE
TI Determination of the D- and L-enantiomers of **modafinil** in human plasma utilizing liquid-liquid extraction and high-performance liquid chromatography.
AU Gorman S.H.
CS S.H. Gorman, Drug Safety/Disposition Department, Cephalon Inc., 145 Brandywine Parkway, West Chester, PA 19380-4245, United States
SO Journal of Chromatography B: Biomedical Sciences and Applications, (1999) 730/1 (1-7).
Refs: 9
ISSN: 0378-4347 CODEN: JCBBEP
PUI S 0378-4347(99)00149-8
CY Netherlands
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB **Modafinil**, DL-2-[(diphenylmethyl)sulfinyl]acetamide (**Provigil**(.RTM.)), which is chiral at its sulfur atom, is a novel wake-promoting agent currently being developed as the racemate in the United States by Cephalon, Inc. In order to characterize the pharmacokinetic properties of each enantiomer, a stereospecific high-performance liquid chromatography (HPLC) method has been developed for simultaneous determination of D- and L-**modafinil** in human plasma. The analytes are extracted from plasma into a mixture of hexane-methylene chloride-triethylamine (55:45:2, v/v/v) and then resolved on an EM Separations ChiraDex(TM) .beta.-**cyclodextrin** column at 12.degree.C using an isocratic mobile phase of 0.020 M, pH 3.0 phosphate buffer-acetonitrile (84:14, v/v). d- and l-**modafinil**, and the internal standard, 3,3-diphenylpropylamine, are monitored by UV detection at 225 nm. The two major circulating metabolites, **modafinil** acid and **modafinil** sulfone, have been shown not to interfere with the assay. Using 0.200 ml of plasma for extraction, the quantifiable range of the assay is 0.100 to 15.0 .mu.g/ml for each enantiomer. The utility of the assay for the characterization of D- and L-**modafinil** pharmacokinetics in humans after single and multiple oral doses of racemic **modafinil** has been demonstrated. Copyright (C) 1999 Elsevier Science B.V.
CT Medical Descriptors:
*drug determination
*enantiomer
liquid liquid extraction
blood analysis
stereospecificity
reproducibility
drug stability

drug blood level
human
oral drug administration
article
priority journal
Drug Descriptors:
***modafinil: CR, drug concentration**
***modafinil: AN, drug analysis**
beta cyclodextrin
RN (**modafinil**) **68693-11-8**; (beta **cyclodextrin**) **7585-39-9**
CN **(1) Provigil**
NP (1) ChiraDex
CO (1) Cephalon
CO (1) EM

L102 ANSWER 5 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **1999114223** EMBASE
TI Open-label, single-dose pharmacokinetic study of **modafinil** tablets: Influence of age and gender in normal subjects.
AU Wang Y.N.; King S.P.; Simcoe D.; Gorman S.; Laughton W.; McCormick G.C.; Grebow P.
CS Dr. Y.N. Wang, Eisai Research Institute, 100 Research Drive, Wilmington, MA 01887, United States
SO Journal of Clinical Pharmacology, (1999) 39/3 (281-288).
Refs: 22
ISSN: 0091-2700 CODEN: JCPCBR
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB An open-label, single-center, single-dose, parallel-group study was performed in healthy young males and females as well as healthy elderly males to examine the influence of age and gender on the pharmacokinetics of **modafinil** following administration of a single 200 mg oral dose. Twelve subjects were enrolled in each of the following three groups: young males, young females, and elderly males. Each fasted (overnight) subject received 2 x 100 mg **modafinil** tablets. Blood and urine samples were collected at various times up to 72 hours postdose for the determination of plasma and urine levels of **modafinil** as well as the acid and sulfone metabolites. The plasma concentrations of the individual isomers, d- and l-**modafinil**, were also determined. Pharmacokinetic parameters were determined by noncompartmental methods. **Modafinil** was well tolerated at a single oral dose of 200 mg. The most commonly reported adverse events were headache, fever, pharyngitis, and asthenia. There were no clinically meaningful differences with respect to the incidence rate of treatment-emergent adverse events among the young female, young male, and old male groups. **Modafinil** was rapidly absorbed after oral dosing and slowly cleared (t(1/2) .apprx. 11-14 hr) from the body. **Modafinil** acid was the major urinary metabolite, which accounted for 35% to 60% of the dose. Results from this study indicated that there were age and gender effects on **modafinil** clearance processes. In this regard, the clearance rate of **modafinil** in males decreased with age while young females cleared **modafinil** at a faster rate than young males. Stereospecific pharmacokinetics of **modafinil** were also demonstrated. The d-**modafinil** was eliminated three times faster than the l-**modafinil**.
CT Medical Descriptors:
***drug absorption**

***drug clearance**
***drug elimination**
age
sex difference
drug urine level
drug blood level
metabolite
headache: SI, side effect
fever: SI, side effect
pharyngitis: SI, side effect
asthenia: SI, side effect
narcolepsy: DT, drug therapy
stereospecificity
enantiomer
pulse rate
area under the curve
distribution volume
human
male
female
clinical article
normal human
clinical trial
aged
adult
oral drug administration
article
Drug Descriptors:
***modafinil: AE, adverse drug reaction**
***modafinil: CT, clinical trial**
***modafinil: CR, drug concentration**
***modafinil: DT, drug therapy**
***modafinil: PK, pharmacokinetics**
sulfone derivative: CR, drug concentration
sulfone derivative: PK, pharmacokinetics
acetamide derivative: CR, drug concentration
acetamide derivative: PK, pharmacokinetics
modafinil acid: CR, drug concentration
modafinil acid: PK, pharmacokinetics
modafinil sulfone: CR, drug concentration
modafinil sulfone: PK, pharmacokinetics
RN (**modafinil**) **68693-11-8**

L102 ANSWER 6 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **1999041047** EMBASE
TI A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of **modafinil** tablets in healthy male volunteers.
AU Wang Y.N.; Simcoe D.; Hartman L.N.; Laughton W.B.; King S.P.; McCormick G.C.; Grebow P.E.
CS Dr. Y.N. Wang, Eisai Research Institute, 100 Research Drive, Wilmington, MA 01887, United States
SO Journal of Clinical Pharmacology, (1999) 39/1 (30-40).
Refs: 23
ISSN: 0091-2700 CODEN: JCPCBR
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LA English
SL English

AB A randomized, double-blind, placebo-controlled, ascending-dose study was conducted to evaluate the pharmacokinetic and safety profiles of increasing **modafinil** doses (200 mg, 400 mg, 600 mg, 800 mg) administered orally over a 7-day period in normal healthy male volunteers. Eight subjects (six **modafinil**; two placebo) were randomized to each of the four dose groups. **Modafinil** or a placebo was administered once daily for 7 days. Serial blood samples were obtained following administration of the day 1 and day 7 doses for characterization of pharmacokinetics, and trough samples were obtained prior to dosing on days 2 through 6 to assess the time to reach the steady state. Pharmacokinetic parameters were calculated using noncompartmental methods. **Modafinil** steady state was reached after three daily doses. **Modafinil** pharmacokinetics were dose and time independent over the range of 200 mg to 800 rag. Steady-state pharmacokinetics of **modafinil** were characterized by a rapid oral absorption rate, a low plasma clearance of .apprx.50 mL/min, a volume of distribution of .apprx.0.8 L/kg, and a long half-life of .apprx.15 hr. **Modafinil** was primarily eliminated by metabolism. **Modafinil** acid was the major urinary metabolite. Stereospecific pharmocokinetics of **modafinil** were demonstrated. The d-**modafinil** enantiomer was eliminated at a threefold faster rate than 1-**modafinil**. **Modafinil** 200 mg, 400 mg, and 600 mg doses were generally well tolerated. The **modafinil** 800 mg dose panel was discontinued after 3 days of treatment due to the observation of increased blood pressure and pulse rate. The safety data from this study suggest that the maximum tolerable single daily oral **modafinil** dose, without titration, may be 600 mg.

CT Medical Descriptors:
***pharmacokinetics**
*drug tolerability
tablet
dose response
drug absorption
plasma clearance
drug distribution
drug half life
drug elimination
drug metabolism
enantiomer
hypertension: SI, side effect
tachycardia: SI, side effect
drug structure
drug blood level
area under the curve
headache: SI, side effect
insomnia
volunteer
human
male
human experiment
normal human
clinical trial
randomized controlled trial
double blind procedure
controlled study
adult
oral drug administration
article
Drug Descriptors:
***modafinil: AE, adverse drug reaction**
***modafinil: CT, clinical trial**
***modafinil: AN, drug analysis**
***modafinil: CR, drug concentration**

***modafinil: DO, drug dose**
***modafinil: PR, pharmaceutics**
***modafinil: PK, pharmacokinetics**
*placebo
***modafinil acid: AN, drug analysis**
***modafinil acid: CR, drug concentration**
***modafinil acid: PK, pharmacokinetics**
*drug metabolite: AN, drug analysis
*drug metabolite: CR, drug concentration
***drug metabolite: PK, pharmacokinetics**
***modafinil sulfone: AN, drug analysis**
***modafinil sulfone: CR, drug concentration**
***modafinil sulfone: PK, pharmacokinetics**
RN (**modafinil**) **68693-11-8**

L102 ANSWER 7 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **1998016978** EMBASE
TI **Modafinil**: A novel stimulant for the treatment of narcolepsy.
AU Scammell T.E.; Matheson J.
CS T.E. Scammell, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, United States
SO Expert Opinion on Investigational Drugs, (1998) 7/1 (99-112).
Refs: 65
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 007 Pediatrics and Pediatric Surgery
024 Anesthesiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Excessive daytime sleepiness (EDS) is a common and debilitating symptom of narcolepsy and other sleep disorders. **Modafinil** is a novel stimulant which effectively treats EDS, yet lacks many of the undesirable side-effects commonly encountered with currently available compounds. The specific mode of action of **modafinil** is not well understood, but it may promote sleep by indirectly influencing adrenergic or GABAergic neurotransmission. **Modafinil**-induced wakefulness is not associated with rebound hypersomnolence or the potential for abuse as is often encountered with other stimulants such as amphetamines. At typical therapeutic doses, **modafinil** may produce dry mouth but generally has a low incidence of minor side-effects. Many preclinical and clinical studies have demonstrated the effectiveness of **modafinil** in promoting wakefulness and vigilance in normal subjects and in those with EDS. **Modafinil** significantly improves the EDS of narcolepsy and also may improve the EDS of idiopathic hypersomnia and obstructive sleep apnoea. **Modafinil**'s low prevalence of side-effects, minimal potential for abuse, and lack of rebound hypersomnia indicated that it has potential to become a widely prescribed drug for the treatment of narcolepsy.
CT Medical Descriptors:
*narcolepsy: DT, drug therapy
*sleep disorder: DT, drug therapy
somnolence
drug effect
drug efficacy
drug safety
drug tolerability
wakefulness
drug mechanism
drug information

xerostomia: SI, side effect
drug metabolism
nausea: SI, side effect
headache
cardiovascular effect
anxiety
hypersomnia
human
oral drug administration
clinical trial
review
Drug Descriptors:
***modafinil: AE, adverse drug reaction**
***modafinil: CT, clinical trial**
***modafinil: DT, drug therapy**
***modafinil: TO, drug toxicity**
***modafinil: PK, pharmacokinetics**
***modafinil: PD, pharmacology**
central stimulant agent
RN **(modafinil) 68693-11-8**

L102 ANSWER 8 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **97020246** EMBASE
DN **1997020246**
TI Pharmacokinetic profile of **modafinil**.
AU Moachon G.; Kanmacher I.; Clenet M.; Matinier D.
CS G. Moachon, Centre Recherches du Lab. L. Lafon, BP 22, 94701 Maisons-Alfort, France
SO Drugs of Today, (1996) 32/SUPPL. I (23-33).
Refs: 9
ISSN: 0025-7656 CODEN: MDACAP
CY Spain
DT Journal; General Review
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The pharmacokinetics of **modafinil** have been studied in mouse, rat, rabbit, dog and humans in a large range of doses. In humans **modafinil** exhibits linear kinetics, with plasma concentrations and AUC increasing proportionally with dose after either single or repeated administration. The t(1/4) ranges from 10-15 h and allows a once- or twice-daily administration. The extent of plasma protein binding is approximately 60%. **Modafinil** is extensively metabolized. The percentage of unchanged **modafinil** excreted in the urine is low (< 10% of the administered dose). The main metabolite, **modafinil** acid, is inactive and excreted unconjugated in the urine (40-60% o the administered dose). The pharmacokinetics of **modafinil** are not modified by food but are altered in patients with severe hepatic and renal disease. Therefore, a 50% dose reduction is recommended in patients with hepatic insufficiency or chronic renal failure.
CT Medical Descriptors:
*bioavailability
*drug blood level
animal experiment
area under the curve
dog
drug absorption
drug distribution
drug elimination
drug half life
drug metabolism
drug protein binding

drug structure
drug urine level
human
kidney failure
liver failure
mouse
nonhuman
pharmacokinetics
rabbit
rat
review
Drug Descriptors:
***modafinil: PD, pharmacology**
***modafinil: PK, pharmacokinetics**
***modafinil: CR, drug concentration**
drug metabolite: CR, drug concentration
RN (**modafinil**) **68693-11-8**

L102 ANSWER 9 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **96203540** EMBASE
DN **1996203540**
TI Pharmacokinetic profile of **modafinil**.
AU Moachon G.; Kanmacher I.; Clenet M.; Matinier D.
CS Centre de Recherches, Laboratoire L. Lafon, BP 22,94701 Maisons-Alfort, France
SO Drugs of Today, (1996) 32/4 (327-337).
ISSN: 0025-7656 CODEN: MDACAP
CY Spain
DT Journal; General Review
FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The pharmacokinetics of **modafinil** have been studied in mouse, rat, rabbit, dog and humans in a large range of doses. In humans **modafinil** exhibits linear kinetics, with plasma concentrations and AUC increasing proportionally with dose after either single or repeated administration. The t(1/4) ranges from 10-15 h and allows a once- or twice-daily administration. The extent of plasma protein binding is approximately 60%. **Modafinil** is extensively metabolized. The percentage of unchanged **modafinil** excreted in the urine is low (< 10% of the administered dose). The main metabolite, **modafinil** acid, is inactive and excreted unconjugated in the urine (40-60% of the administered dose). The pharmacokinetics of **modafinil** are not modified by food but are altered in patients with severe hepatic and renal disease. Therefore, a 50% dose reduction is recommended in patients with hepatic insufficiency or chronic renal failure.
CT Medical Descriptors:
***drug metabolism**
*liver metabolism
animal experiment
brain
dog
dose response
drug blood level
drug tissue level
enzyme induction
guinea pig
high performance liquid chromatography
human
human experiment
in vitro study

intraperitoneal drug administration
intravenous drug administration
kidney failure
mouse
nonhuman
normal human
oral drug administration
rabbit
rat
review
ultraviolet spectrophotometry
Drug Descriptors:
*central stimulant agent: CR, drug concentration
***central stimulant agent: PK, pharmacokinetics**
*central stimulant agent: AD, drug administration
*central stimulant agent: CM, drug comparison
*central stimulant agent: DO, drug dose
*central stimulant agent: PD, pharmacology
*central stimulant agent: AN, drug analysis
***modafinil: PD, pharmacology**
***modafinil: AD, drug administration**
***modafinil: CM, drug comparison**
***modafinil: DO, drug dose**
***modafinil: CR, drug concentration**
***modafinil: PK, pharmacokinetics**
***modafinil: AN, drug analysis**
diazepam: DO, drug dose
diazepam: PD, pharmacology
diazepam: CM, drug comparison
phenobarbital: PD, pharmacology
phenobarbital: DO, drug dose
phenobarbital: CM, drug comparison
RN (**modafinil**) **68693-11-8**; (diazepam) 439-14-5; (phenobarbital) 50-06-6, 57-30-7, 8028-68-0
CN **Modiodal; Crl 40476**

L102 ANSWER 10 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN **91178302** EMBASE
DN **1991178302**
TI **Modafinil**: The unique properties of a new stimulant.
AU Lyons T.J.; French J.
CS Aerospace Medical Science and Technology, Headquarters, Human Systems Division, HG HSD/XAPM, Brooks Air Force Base, TX 78235, United States
SO Aviation Space and Environmental Medicine, (1991) 62/5 (432-435).
ISSN: 0095-6562 CODEN: ASEMCG
CY United States
DT Journal; Article
FS 035 Occupational Health and Industrial Medicine
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB **Modafinil**, a novel stimulant which has several remarkable features that distinguish it from other stimulants, has been developed by Lafon, a French pharmaceutical company. Unlike the amphetamines, for example, **modafinil** is reported to have minimal peripheral side effects at therapeutic doses. It also appears to have a low abuse potential, does not interfere with normal sleep, and does not seem to produce tolerance. It improves vigilance especially in sleep-deprived subjects. It has been used clinically for up to 3 years in the treatment of narcolepsy and idiopathic hypersomnia. It could be an ideal replacement for amphetamine in short-term operations in which fatigue might threaten the successful completion of a mission. We recommend that military

laboratories experienced in studying sustained performance include **modafinil** or perhaps a more selective alpha 1 receptor agonist in their investigations.
CT Medical Descriptors:
*airplane crew
*fatigue
*insomnia: ET, etiology
*narcolepsy: ET, etiology
*sleep disorder
aerospace medicine
article
human
Drug Descriptors:
*central stimulant agent: PD, pharmacology
*central stimulant agent: DT, drug therapy
***modafinil: PD, pharmacology**
***modafinil: DT, drug therapy**
RN (**modafinil**) **68693-11-8**
CO Lafon

=> fil wpix
FILE 'WPIX' ENTERED AT 15:36:30 ON 09 OCT 2002
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FILE LAST UPDATED: 07 OCT 2002 <20021007/UP>
MOST RECENT DERWENT UPDATE 200264 <200264/DW>
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>>> SLART (Simultaneous Left and Right Truncation) is now available in the /ABEX field. An additional search field /BIX is also provided which comprises both /BI and /ABEX <<<

>>> The BATCH option for structure searches has been enabled in WPINDEX/WPIDS and WPIX <<<

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>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d all abeq tech abex tot

L120 ANSWER 1 OF 2 WPIX (C) 2002 THOMSON DERWENT
AN 2002-590702 [63] WPIX
DNC C2002-167156
TI Complex for treating e.g. sleepiness comprises **modafinil** compound and **cyclodextrin**.
DC B05 B07
IN JACOBS, M J; PATEL, P R
PA (CEPH-N) CEPHALON INC
CYC 99
PI WO 2002056915 A2 20020725 (200263)* EN 25p A61K047-40 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO
RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

ADT WO 2002056915 A2 WO 2001-US49189 20011219

PRAI US 2001-23441 20011218; US 2000-256681P 20001219

IC ICM **A61K047-40**
ICS A61K031-165

AB WO 200256915 A UPAB: 20021001
NOVELTY - A complex and a composition (I) comprise a **modafinil** compound (a) and a **cyclodextrin** (b).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) An aqueous pharmaceutical composition comprising a **modafinil** compound (a) and a **cyclodextrin** (b); and
(2) Preparation of the complex by contacting (a) with (b) in an aqueous medium.
ACTIVITY - Antiparkinsonian; Cerebroprotective; Nootropic; Tranquilizer.
MECHANISM OF ACTION - Promoter of wakefulness; Appetite or weight gain stimulator.
USE - For treating sleepiness, tiredness, Parkinson's disease, cerebral ischemia, stroke, sleep apneas, eating disorders, attention deficit hyperactivity disorder, cognitive dysfunction or fatigue and for the promotion of wakefulness, stimulation of appetite or stimulation of weight gain (all claimed).
ADVANTAGE - The composition provides at least 25 (preferably 50 especially 50 - 400 particularly 50 - 200 more particularly 50 - 100)% increase in the blood serum level of (a) in mammals within the first hour of administration relative to a solid dose of (a). The complex provides enhanced aqueous solubility of (a) and enhanced pharmacological properties. The complex can provide oral bioavailability of (a) and can effectively taste-mask (a) thus providing palatable liquid compositions.
Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: **B04-C02B1**; B10-A10; B14-E11; B14-E12; B14-J01A3; B14-N16

TECH UPTX: 20021001
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: (a) has an aqueous solubility of at least 10 (preferably at least 20) mg/ml. The molar ratio of (b) to (a) is 10:1 - 0.8:1 (preferably 1:1).
Preferred Complex: The complex is an inclusion complex and is a solid or in solution. The composition comprises (a) in an aqueous 50 % hydroxypropyl-beta-**cyclodextrin** solution. The composition has substantially a blood serum profile as given in the specification. (I) is taste masked.
Preferred Method: The complex is dried and is isolated as a solid.

ABEX
SPECIFIC COMPOUNDS - Modafinil (2-(benzhydryl-sulfinyl)acetamide or 2-((diphenylmethyl)sulfinyl)acetamide) is specifically claimed as (a). alpha-, beta-, gamma-Cyclodextrin, dimethyl-beta-cyclodextrin, trimethyl-beta-cyclodextrin, 2-hydroxymethyl-beta-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, 3-hydroxypropyl-beta-cyclodextrin, beta-cyclodextrin sulfonate and beta-cyclodextrin sulfobutyl ether are specifically claimed as (b).

ADMINISTRATION - The composition contains at least one unit dose of (a) in an amount of 200 (preferably 100) mg. The composition is a solid in the form of a tablet or a capsule or a syrup or an elixir and is administered orally (all claimed). The dosage of (a) can also be 0.01 - 100 mg/kg or 0.1 - 2000 mg (preferably 1 - 500 mg one to four times a day especially 10 - 400 mg one or two times a day.

EXAMPLE - A solution of hydroxypropyl-beta-cyclodextrin (3.53 g) in water

(3.54 g) was stirred with warming at 60 - 70 degrees C. Micronized modafinil (0.1815 g) was added to the resulting solution and stirred until no particulate matter remained. Cooling to room temperature gave the product solution (nearly 6 ml) with no precipitate formation and a modafinil concentration of approximately 30 mg/ml. The solution was administered on rats. The blood serum levels after 0.25/0.5/1/2/4/6 hours were 11.65/21.3/19.7/7.1/1.8/0.5 respectively.

L120 ANSWER 2 OF 2 WPIX (C) 2002 THOMSON DERWENT
AN 1994-316724 [39] WPIX
DNC C1994-144296
TI Particles contg. an active ingredient e.g. for therapeutic use - made by extruding a pasty aq. mixt. of the active material and a hydrophilic carrier, comminuting the extrudate and freeze drying the particles.
DC B07 C07 D13 D21
IN JACQUOT-LEYDER, J; NGUYEN, T
PA (LAFO) LAB LAFON SA L
CYC 20
PI WO 9421371 A1 19940929 (199439)* FR 37p B01J013-04
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: CA JP US
FR 2702968 A1 19940930 (199439) 32p B01J002-00
EP 690747 A1 19960110 (199607) FR B01J013-04
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 08507940 W 19960827 (199702) 36p A61J003-06
EP 690747 B1 19970528 (199726) FR 19p B01J013-04
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69403463 E 19970703 (199732) B01J013-04
ES 2105663 T3 19971016 (199748) B01J013-04
US 5843347 A 19981201 (199904) B01J002-04
ADT WO 9421371 A1 WO 1994-FR281 19940315; FR 2702968 A1 FR 1993-3316 19930323; EP 690747 A1 EP 1994-909968 19940315, WO 1994-FR281 19940315; JP 08507940 W JP 1994-520710 19940315, WO 1994-FR281 19940315; EP 690747 B1 EP 1994-909968 19940315, WO 1994-FR281 19940315; DE 69403463 E DE 1994-603463 19940315, EP 1994-909968 19940315, WO 1994-FR281 19940315; ES 2105663 T3 EP 1994-909968 19940315; US 5843347 A Cont of WO 1994-FR281 19940315, Cont of US 1995-530293 19950919, US 1997-906004 19970804
FDT EP 690747 A1 Based on WO 9421371; JP 08507940 W Based on WO 9421371; EP 690747 B1 Based on WO 9421371; DE 69403463 E Based on EP 690747, Based on WO 9421371; ES 2105663 T3 Based on EP 690747
PRAI FR 1993-3316 19930323
REP DE 204596; GB 2004182; GB 2133983; US 4230687; EP 438359
IC ICM A61J003-06; B01J002-00; B01J002-04; B01J013-04
ICS A23P001-02; A61K009-14; B01J002-18; B01J013-02; C08J009-28; F26B005-06
AB WO 9421371 A UPAB: 19941122
Process for preparing particles useful e.g. for therapeutic purposes, each particle comprising an excipient forming a matrix and at least one active ingredient uniformly distributed throughout the matrix, comprises producing dry core bodies of uniform (esp. spherical) shape by extrusion or moulding followed by lyophilisation, after which the dry core bodies can be individually coated or incorporated into a more complex preparation.

In a pref. process, a pasty mixt. of the excipient and the active material having a viscosity at ambient temp. of less than 1 Pa.s is extruded and the extrudate is sepd. into wet particles having a size of 0.01-5mm. The particles are frozen by contact with an inert fluid at a temp. of below 0 deg.C, then the frozen particles are freeze-dried. In a specific case, the extrudate is divided into particles by vibrating the extrusion nozzle, e.g. at 50-10,000 Hz and the particles are frozen by falling under gravity in counterflow to a current of inert gas at a temp. below 0 deg.C. The frozen particles are dried by freeze drying at temps. e.g. of -18 to -80 deg.C, esp. -30 to -50 deg.C.

USE/ADVANTAGE - For prodn. of small particles, esp. microspheres, having a maximum dimension of 0.05-5mm and contg. therapeutically, cosmetically, dietetically or nutritionally active ingredient(s) for use by humans or animals. The particulate prods. provide good chemical and physical stability of active ingredients during storage, improved bioavailability of the active ingredients, and allow effective subsequent coating of the particles.
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: B04-C02; C04-C02; B04-C03; C04-C03; B04-N02; C04-N02; B10-D03; C10-D03; B11-C05; C11-C05; B11-C09; C11-C09; B12-M11; C12-M11; B12-M11E; C12-M11E; D03-H01; D08-B
ABEQ EP 690747 B UPAB: 19970626
A process for the preparation of particles each comprising an excipient forming a matrix and at least one active ingredient uniformly distributed in the mass of said matrix, said process, which comprises the operations of extrusion and then lyophilization, being characterised in that it comprises the steps consisting of: (1 degree) thre preparation of a homogeneous mixture from (a) at least one active ingredient, (b) a physiologically acceptable hydrophilic excipient, and (c) water; to give a pasty mixture with a viscosity below 1 Pa.s, measured at room temperature (15-20 degree C); (2 degree) the extrusion of the resulting homogeneous mixture and the cuttng of the extrudate to give moist particles; (3 degree) the freezing of the resulting particles as they fall under gravity through a stream of inert gas at a temperature below degree C, and (4 degree) the drying of said particles by freeze drying.
Dwg.0/3

=> d hit 2

L120 ANSWER 2 OF 2 WPIX (C) 2002 THOMSON DERWENT
DRN 0038-U; 0104-U; 0241-U; 0290-U; 0758-U; 0856-U; 1835-U; 1849-U; 1852-U; **1856-U**; 1857-U; 2029-U; 2044-U
M2 *09* DCN: **R04818-M**
M2 *13* DCN: R04846-M; R18766-M; **R22184-M**

=> e r04818+all/dcn
E1 466 --> R04818/DCN
E2 UF CYCLODEXTRIN, GAMMA/DCN
********* END***

=> e r01856+all/dcn
E1 852 --> R01856/DCN
E2 UF CYCLODEXTRIN, BETA-/DCN
E3 UF CYCLOHEPTAAMYLOSE/DCN
********* END***

=> e r22184+all/dcn
E1 23 --> R22184/DCN
E2 UF MODAFINIL/DCN
********* END***

=> d his

(FILE 'HOME' ENTERED AT 13:42:03 ON 09 OCT 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 13:42:25 ON 09 OCT 2002
E MODAFINIL/CN
L1 1 S E3

```
L2            1 S E4
L3          431 S C15H15NO2S/MF AND 46.150.18/RID AND 2/NR
L4           37 S L3 AND ACETAMIDE
L5            4 S L4 AND DIPHENYLMETHYL
L6            3 S L5 NOT HYDROXY
L7            3 S L1,L6 AND MODAFINIL
L8          333 S C15H14O3S/MF AND 46.150.18/RID AND 2/NR
L9            3 S L8 AND ACETIC ACID AND DIPHENYLMETHYL
L10           3 S L2,L9
                SEL RN L7
L11           5 S E1-E3/CRN
                SEL RN L10
L12           2 S E4-E6/CRN

     FILE 'HCAOLD' ENTERED AT 14:16:11 ON 09 OCT 2002
L13           0 S L7
L14           0 S L11

     FILE 'HCAPLUS' ENTERED AT 14:16:11 ON 09 OCT 2002
L15           1 S L11
L16         143 S L7
L17         157 S MODAFINIL OR PROVIGIL OR MODIODAL OR CRL40476 OR CRL()(40476
L18         160 S L16,L17
L19           3 S L18 AND ?CYCLODEXTRIN?

     FILE 'REGISTRY' ENTERED AT 14:21:31 ON 09 OCT 2002
L20           6 S 12619-70-4 OR 10016-20-3 OR 7585-39-9 OR 17465-86-0 OR 85220-
L21       22279 S (13750 OR 14099 OR 14246 OR 30188 OR 57602)/RID
L22       23429 S ?CYCLODEXTRIN?/CNS
L23       23725 S L21,L22 NOT L20

     FILE 'HCAPLUS' ENTERED AT 14:24:01 ON 09 OCT 2002
L24       14041 S L20
L25       10005 S L23
L26           2 S L18 AND L24,L25
L27           3 S L15,L19,L26
L28           2 S L27 NOT CHROMATOGRAPHY/TI
                E JACOBS M/AU
L29         170 S E3,E15-E18
                E JACOBS MARTIN/AU
L30          19 S E3,E8,E9
                E MARTIN J/AU
L31        4190 S E3-E82,E94-E96
                E PIYUSH P/AU
L32           1 S E2
                E PATEL P/AU
L33         812 S E3-E24
                E PATEL PIYUSH/AU
L34          33 S E3-E8
L35           3 S L18 AND L29-L34
                E CEPHALON/PA,CS
L36         270 S E3-E23
L37          21 S L18 AND L36
L38           2 S L35,L37 AND (L24,L25 OR ?CYCLODEXTRIN?)
L39           5 S L26-L28,L35,L38
L40           1 S L39 AND L11
L41           5 S L39,L40
                E DRUG BIOAVAILABILITY/CT
                E E3+ALL
L42       13090 S E3
                E E6+ALL
L43        3389 S E5,E4+NT
                E E9+ALL
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L44         6372 S E2+NT
                 E PHARMACOKINETICS/CT
                 E E3+ALL
L45        12487 S E2+NT
                 E E11+ALL
L46        57131 S E3+NT
L47           12 S L18 AND L42-L46
                 SEL DN AN 8
L48            1 S L47 AND E1-E3
L49           97 S L7 (L) (ADV OR BCP OR BPR OR BSU OR DMA OR MFM OR PAC OR PKT)
L50           97 S L49 AND L18
L51            2 S L41,L48 AND L50
L52            6 S L41,L48,L51
L53           85 S L50 NOT L52,L47
                 SEL DN AN 31 38 50 52 55 58 62 63 71 72
L54           10 S L53 AND E4-E33
L55           16 S L52,L54
L56           59 S L18 NOT L47-L55
                 SEL DN AN 22 25
L57            2 S L56 AND E34-E39
L58           18 S L55,L57 AND L15-L19,L24-L57
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:04:31 ON 09 OCT 2002
L59           14 S E40-E53
L60            8 S L59 AND L7,L11
L61            6 S L59 AND L20,L23 NOT L60

     FILE 'REGISTRY' ENTERED AT 15:06:09 ON 09 OCT 2002

     FILE 'HCAPLUS' ENTERED AT 15:06:47 ON 09 OCT 2002

     FILE 'EMBASE' ENTERED AT 15:07:30 ON 09 OCT 2002
L62          344 S L7
L63            0 S L11
L64          352 S L17
L65          352 S L62,L64
L66            1 S L65 AND L20,L61
L67            1 S L65 AND ?CYCLODEXTRIN?
L68            1 S L66,L67
                 E DRUG STABILITY/CT
                 E E3+ALL
L69        19140 S E8+NT
                 E DRUG BIOAVAILABILITY/CT
L70        11287 S E3+NT
                 E DRUG ABSORPTION/CT
L71        36538 S E3+NT
                 E DRUG METABOLISM/CT
L72        96843 S E3+NT
                 E PHARMACOKINETICS/CT
                 E E3+ALL
L73       346337 S E4+NT
L74      1680954 S E3+NT
L75          237 S L65 AND L69-L74
L76          344 S MODAFINIL/CT
L77            2 S L76 AND L69
L78            5 S L76 AND L70
L79           12 S L76 AND L71
L80           19 S L76 AND L72
L81           48 S L76 AND L73
L82           28 S L77-L80
L83           26 S L81 AND L82
L84           22 S L81 NOT L83
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L85          28 S L82,L83
                SEL DN AN 18 20 24 25 26
L86           5 S L85 AND E1-E7
L87           6 S L68,L86
L88         146 S (MODAFINIL(L)(PD OR PK))/CT
                E MODAFINIL/CT
L89          73 S E12,E13
L90          37 S E24,E27,E29,E30
L91         151 S L88-L90 NOT L77-L87
L92          37 S L91 NOT AB/FA
L93         114 S L91 NOT L92
L94          93 S L76/MAJ AND L93
                SEL DN AN 2 90
L95           2 S L94 AND E1-E3
L96           8 S L87,L95
L97          21 S L93 NOT L94
L98           9 S L96,L77
L99          12 S L79 NOT L77
                SEL DN AN 4 7 9 11
L100          4 S L99 AND E4-E8
L101         10 S L98,L100
L102         10 S L101 AND L65

     FILE 'EMBASE' ENTERED AT 15:29:29 ON 09 OCT 2002

     FILE 'DRUGLAUNCH' ENTERED AT 15:29:40 ON 09 OCT 2002
                E MODAFINIL
L103         26 S E3
L104         26 S L17
L105         26 S L103,L104
L106          0 S L105 AND (CYCLODEXTRIN OR CYCLO DEXTRIN)

     FILE 'WPIX' ENTERED AT 15:31:10 ON 09 OCT 2002
L107         22 S L17
                E MODAFINIL/DCN
                E E3+ALL
L108         23 S E2
L109         25 S L107,L108
L110          1 S L109 AND ?CYCLODEXTRIN?
L111          0 S L109 AND ?CYCLO DEXTRIN?
L112          2 S L109 AND (R24032 OR R04817 OR R01856 OR R04818 OR R17245 OR R
L113          1 S L109 AND 1856/DRN
L114          1 S L109 AND A61K047-40/IC,ICM,ICS,ICA,ICI
L115          1 S L109 AND (B04-C02B1 OR C04-C02B1)/MC
L116          2 S L110,L112-L115
                E R16387+ALL/DCN
L117         27 S E1
                E R12786+ALL/DCN
L118          4 S E1
L119          1 S L109 AND L117,L118
L120          2 S L116,L119

     FILE 'WPIX' ENTERED AT 15:36:30 ON 09 OCT 2002
                E R04818+ALL/DCN
                E R01856+ALL/DCN
                E R22184+ALL/DCN
                E R1857+ALL/DCN
                E R01857+ALL/DCN
                E R04846+ALL/DCN
                E R18766+ALL/DCN
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